Clinical trial results:
A Multicenter, Open-label, Single-Arm Study to Evaluate the Safety, Compliance and Pharmacokinetics associated with the use of a Combined Oral Contraceptive Containing 15 mg Estetrol monohydrate and 3 mg Drospirenone in Post-menarchal Female Adolescents for 6 cycles

Summary

EudraCT number	2019-003002-27
Trial protocol	FI EE LV SE PL
Global end of trial date	24 November 2023

Results information

Result version number	v1 (current)
This version publication date	06 June 2024
First version publication date	06 June 2024

Trial information

Trial identification

Sponsor protocol code	MIT-Es001-C303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04792385
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Estetra SRL
Sponsor organisation address	Rue Saint-Georges 5/7, Liège, Belgium, 4000
Public contact	Clinical Study Leader, Estetra SRL, +32 43492822, Clinical.Trials@mithra.com
Scientific contact	Clinical Study Leader, Estetra SRL , +32 43492822, Clinical.Trials@mithra.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001332-PIP01-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety profile of E4/DRSP 15/3 mg in post-menarchal subjects aged 12 to 17 years and 2 months (inclusive) at the time of signing the informed consent (IC).

This study was a Phase 3, multicenter, open-label, single-arm study. Subjects were enrolled to receive once daily E4/DRSP 15/3 mg for six (6) 28-day cycles in a 24/4-day regimen (i.e. 24 days of active tablets followed by 4 days of placebo tablets [4-day hormone-free interval]). The study contained a sub-study for the analysis of Pharmacokinetics (PK) parameters of E4/DRSP. The study included 6 visits: Visit 1 (Screening Visit), Visit 2 (Subject Enrolment Visit), (Visit 3, Visit 4, Visit 5/Early Termination (ET) Visit) on-treatment visits, and Visit 6 post-treatment visit (planned over about 6 months). The site also completed an 'Eligibility Confirmation' phone call to the subject after Visit 1 and a follow-up call after Visit 2, within 7 days following the first intake of the investigational product (IP) .

Protection of trial subjects:

This study was conducted in accordance with the CSP (and CSP amendments), and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, ICH GCP1, 21 CFR 50 Protection of Human Rights, Council for International Organizations of Medical Sciences International Ethical Guidelines, 21 CFR 56 IRB, and other applicable laws and regulations of the countries in which the study was conducted. These procedures served to ensure the protection of the rights and the integrity of the subjects, adequate and correct conduct of all study procedures, adequate data collection, adequate documentation, and adequate data verification. The Investigator and any designee agreed to conduct the clinical study in compliance with the protocol agreed with the Sponsor and approved by the IEC.

Prior to or at the beginning of the Screening Visit, the Investigator or designee ensured that each subject was given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study, and the Investigator or the designee answered all questions the subjects might have had to her full satisfaction. The subjects had sufficient time for consideration of their participation in the study and were notified that they were free to discontinue their participation at any time.

Post-treatment contraceptive counselling was given to each subject at Visit 5 or at the ET Visit in case of premature study termination.

Background therapy: -

Evidence for comparator:

Not applicable, as no comparators were used in this study.

LIST OF ABBREVIATIONS IN THIS STUDY ENTRY

AE=Adverse event
COC=Combined oral contraceptive
DRSP=Drospirenone
E4=Estetrol monohydrate
IC=Informed consent
IP=Investigational product
VAS=Visual Analogue Scale; VAS score=[0 no hurt – 10 hurts worst]

Actual start date of recruitment	28 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Sweden: 20
Country: Number of subjects enrolled	Estonia: 20
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	Latvia: 15
Country: Number of subjects enrolled	Georgia: 25
Worldwide total number of subjects	112
EEA total number of subjects	87

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	112
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Female subjects recruited for this single-arm open-label study, according to the Inclusion/Exclusion criteria. Overall, 112 subjects were enrolled into the study and of these, 105 received at least 1 dose of the investigational product (IP).

Pre-assignment

Screening details:

Enrolled in this study were post-menarchal female subject requesting COC either for contraceptive or for therapeutic use. They were aged 12 to 17 years and 2 months (inclusive) at the time of signing the Informed Consent.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The study was not blinded (open-label).

Arms

Arm title	Estetrol / Drospirenone (E4/DRSP)

Arm description:

This is a single-arm open-label study. Treatment consisted of Estetrol 15 mg /Drospirenone 3 mg (E4/DRSP) tablet. Treatment compliance was assessed based on the data entered by the subject in the e-diary.

Arm type	Experimental
Investigational medicinal product name	E4/DRSP
Investigational medicinal product code	
Other name	Estetrol, Drospirenone
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The investigational products is an E4/DRSP (Estetrol 15 mg / Drospirenone 3 mg) tablet administered orally for 24 consecutive days, followed by the administration of a placebo tablet for 4 consecutive days. The treatment was taken once a day at approximately the same time of day.

This 28-day cyclic regimen of E4/DRSP (24 days) and placebo (4 days) was taken for 6 consecutive cycles.
Blister pack (PVC/Aluminum), containing 28 tablets (24 pink active and 4 white placebo).

All subjects were instructed to start the investigational product intake on the first day of the next menstrual bleeding. There should be no interruption between two blister packs.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo tablet was administered orally for 4 consecutive days (after having taken 24 consecutive days of the E4/DRSP (Estetrol 15 mg / Drospirenone 3 mg) tablet).
The placebo tablet was taken once a day at approximately the same time of day.

This 28-day cyclic regimen of E4/DRSP (24 days) and placebo (4 days) was taken for 6 consecutive cycles.

Blister pack (PVC/Aluminum) containing 28 tablets (24 pink and 4 white).

All subjects were instructed to start the IP intake on the first day of the next menstrual bleeding. There should be no interruption between two blister packs.

Number of subjects in period 1[1]	Estetrol / Drospirenone (E4/DRSP)
Started	105
Completed	89
Not completed	16
Consent withdrawn by subject	8
Physician decision	1
Adverse event, non-fatal	1
No longer need for COC	2
Lost to follow-up	3
Protocol deviation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Worldwide number of subjects enrolled into the trial are shown in the table (N=112). Inclusion/Exclusion criteria were not met, Consent was withdrawn, and Protocol deviation before treatment administration were the reasons for N=105 subjects who received at least 1 dose of the study drug.

Baseline characteristics

Reporting groups	
Reporting group title	Estetrol / Drospirenone (E4/DRSP)
Reporting group description:	
This is a single-arm open-label study. Treatment consisted of Estetrol 15 mg /Drospirenone 3 mg (E4/DRSP) tablet. Treatment compliance was assessed based on the data entered by the subject in the e-diary.	

Reporting group values	Estetrol / Drospirenone (E4/DRSP)	Total	
Number of subjects	105	105	
Age categorical Units: Subjects			
Adolescents (12-17 years)	105	105	
Age continuous Units: years			
arithmetic mean	15.2		
standard deviation	± 1.21	-	
Gender categorical Units: Subjects			
Female	105	105	
History of Dysmenorrhea Units: Subjects			
Yes	88	88	
NO	17	17	
Subject’s Contraceptive Use Status Units: Subjects			
Starter	96	96	
Switcher	9	9	
Previous use of hormonal contraceptives Units: Subjects			
Yes	21	21	
No	84	84	
Race Units: Subjects			
Asian	1	1	
Black or African American	2	2	
Not collected due to local restrictions	4	4	
White	98	98	
Ethnicity Units: Subjects			
Not Hispanic or Latino	95	95	
Not collected due to local restrictions	10	10	
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	21.2		

standard deviation	± 2.98	-	

End points

End points reporting groups

Reporting group title	Estetrol / Drospirenone (E4/DRSP)

Reporting group description:

This is a single-arm open-label study. Treatment consisted of Estetrol 15 mg /Drospirenone 3 mg (E4/DRSP) tablet. Treatment compliance was assessed based on the data entered by the subject in the e-diary.

Primary: 1_Adverse events (TEAEs) - Any

End point title	1_Adverse events (TEAEs) - Any[1]

End point description:

Treatment-Emergent Adverse Events (TEAEs) - Any.
Results show the number of subjects and the number of any TEAEs.

TEAE: defined as any event that occurred on or after the date of first administration of IP or, the worsening of a pre-existing event after the first administration of IP. Since the starting point for AEs collection was the signing of the IC, and not the start of the study treatment, the AEs recorded prior to first IP intake were designated as AEs while those that occurred or worsened after the initiation of the IP are designated as TEAEs.

Safety analysis set: subjects from the Enrolled population set who received at least one dose of the study treatment. All safety analyses were based on the Safety Population.

End point type	Primary

End point timeframe:

From the day of first intake of the IP to the end of the follow-up period. Maximum overall duration to collect information on TEAEs was 191 days.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified for this primary end point - safety endpoint. All safety and efficacy parameters have been summarized with descriptive statistics that include: the number of subjects, mean, standard deviation, median, minimum, and maximum for continuous variables, and frequencies and percentages for categorical variables.

End point values	Estetrol / Drospirenone (E4/DRSP)			
Subject group type	Reporting group			
Number of subjects analysed	105[2]			
Units: adverse events				
Number of subjects	54			
Number of events	113			

Notes:

[2] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: 2_Adverse events (TEAEs) -- Related to study medication

End point title	2_Adverse events (TEAEs) -- Related to study medication[3]

End point description:

Adverse events (TEAEs) related to study medication.
Results show the number of subjects with TEAEs assessed as related to study medication.

Related AE, was defined as:
- AE follows a reasonable temporal sequence to study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications).

- AE follows a reasonable temporal sequence to study drug administration and is a known reaction to the drug under study or a related chemical group or is predicted by known pharmacology.

- TEAEs are defined in Endpoint 1.

Safety analysis set (defined under End point 1), was used for evaluations.

End point type	Primary

End point timeframe:

From the day of first intake of the IP to the end of the follow-up period. Maximum overall duration to collect information on TEAEs was 191 days.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified for this primary end point - safety endpoint. All safety and efficacy parameters have been summarized with descriptive statistics that include: the number of subjects, mean, standard deviation, median, minimum, and maximum for continuous variables, and frequencies and percentages for categorical variables.

End point values	Estetrol / Drospirenone (E4/DRSP)			
Subject group type	Reporting group			
Number of subjects analysed	105[4]			
Units: AE -- related to study medication				
Number of subjects	12			
Number of events	15			

Notes:

[4] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: 3_Adverse events (TEAEs) -- Classified as severe

End point title	3_Adverse events (TEAEs) -- Classified as severe[5]

End point description:

Adverse events (TEAEs) intensity - assessed as severe.
Results show the number of subjects with TEAEs assessed as severe.

AE Intensity: The intensity of each AE was recorded as shown below:
• Mild: awareness of sign or symptom, but easily tolerated (acceptable).
• Moderate: discomfort to interfere with usual activities (disturbing).
• Severe: incapacity to work or to perform usual activities (unacceptable).

TEAEs are defined in Endpoint 1.
Safety analysis set (defined under End point 1), was used for evaluations.

End point type	Primary

End point timeframe:

From the day of first intake of the IP to the end of the follow-up period. Maximum overall duration to collect information on TEAEs was 191 days.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified for this primary end point - safety endpoint. All safety and efficacy parameters have been summarized with descriptive statistics that include: the number of subjects, mean, standard deviation, median, minimum, and maximum for continuous variables, and frequencies and percentages for categorical variables.

End point values	Estetrol / Drospirenone (E4/DRSP)			
Subject group type	Reporting group			
Number of subjects analysed	105[6]			
Units: AEs classified as severe				
Number of subjects	2			
Number of events	4			

Notes:

[6] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: 4_Treatment compliance -- Overall and Per cycle

End point title	4_Treatment compliance -- Overall and Per cycle

End point description:

Treatment compliance was calculated as a percentage, based on the actual number of tablets reported as taken in the e-diary divided by the expected number of tablets to be taken, and derived for each cycle that the subject started.

Safety analysis set (as defined under end point 1), was used for evaluations of this end point.

The compliance rate of above 100% was not due to the subjects tablet intake being higher as outlined in the protocol. It is attributed to the design of the Claimit e-diary, which incorporated a free text field to enable subjects to record a higher number than 1 tablet intake. This free text field within the module was susceptible to data entry errors, which were irreversible once saved by the user.

End point type	Secondary

End point timeframe:

From the day of first intake of the IP to the end of the follow-up period. Maximum overall duration to collect information on compliance was 191 days.

End point values	Estetrol / Drospirenone (E4/DRSP)			
Subject group type	Reporting group			
Number of subjects analysed	105[7]			
Units: Percent compliance				
median (full range (min-max))				
All cycles (Overall) (N=98)	100 (33.33 to 900.61)			
Cycle 1 (N=72)	100 (90.32 to 354.84)			
Cycle 2 (N=76)	100 (31.82 to 450.00)			

Cycle 3 (N=74)	100 (82.14 to 413.33)			
Cycle 4 (N=65)	100 (96.00 to 414.29)			
Cycle 5 (N=62)	100 (90.32 to 406.45)			
Cycle 6 (N=39)	100 (96.43 to 384.38)			

Notes:

[7] - Safety Population

N=Evaluable number of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: 5_Dysmenorrhea -- Visual Analogue Scale (VAS) score -- Percent change from baseline

End point title	5_Dysmenorrhea -- Visual Analogue Scale (VAS) score -- Percent change from baseline

End point description:

Change from baseline (pre-treatment cycle) to Cycles 1, 3, and 6 in the Visual Analogue Scale (VAS) score of dysmenorrhea and in the number of days with dysmenorrhea.

Dysmenorrhea assessment: the cycle average of the 3 highest VAS scores [0 no hurt – 10 hurts worst] for evaluable Cycles 1, 3, and 6 and the pre-treatment cycle (Baseline) was used for evaluation. The percent change from baseline of average scores was calculated for the mITT population.

Modified Intent-to-treat (mITT) analysis set was used for evaluations: subjects from the Enrolled set who received at least one dose of the study treatment, had at least one evaluable cycle, and had at least one post-baseline efficacy assessment.

Results are presented as percent change from baseline (based on absolute values of the VAS scores).

End point type	Secondary

End point timeframe:

Baseline (pre-treatment cycle), Cycles 1, 3, and 6.

End point values	Estetrol / Drospirenone (E4/DRSP)			
Subject group type	Reporting group			
Number of subjects analysed	83[8]			
Units: percent change from baseline				
median (full range (min-max))				
Cycle 1 (N=65)	6.7 (-100.0 to 400.0)			
Cycle 3 (N=61)	-36.4 (-100.0 to 700.0)			
Cycle 6 (N=35)	-34.8 (-100.0 to 1800.0)			

Notes:

[8] - mITT Population

N=Evaluable number of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: 6_Use of rescue medication for dysmenorrhea - Subjects

End point title	6_Use of rescue medication for dysmenorrhea - Subjects

End point description:

Use of rescue medication for dysmenorrhea - Number of subjects.

Subjects recorded their use of medication for the relief of dysmenorrheal pain in the e-diary. This was done daily during the pre-treatment cycle (baseline), Cycle 1, Cycle 3, and Cycle 6. If medication was used the type and dose of medication were recorded.

Subjects with at least one use of rescue medication by cycle in the mITT population were evaluated.

End point type	Secondary

End point timeframe:

Baseline to the end of the study (Cycle 1 to Cycle 6).

End point values	Estetrol / Drospirenone (E4/DRSP)			
Subject group type	Reporting group			
Number of subjects analysed	84[9]			
Units: subjects				
Baseline (N=83)	53			
Cycle 1 (N=71)	40			
Cycle 2 (N=45)	11			
Cycle 3 (N=68)	26			
Cycle 4 (N=33)	1			
Cycle 5 (N=20)	5			
Cycle 6 (N=38)	12			

Notes:

[9] - mITT Population

N=Evaluable number of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: 7_Dysmenorrhea -- Use of rescue medication -- Days -- Change from baseline

End point title	7_Dysmenorrhea -- Use of rescue medication -- Days -- Change from baseline

End point description:

Use of rescue medication for dysmenorrhea - Number of days - Change from baseline

Subjects recorded their use of medication for the relief of dysmenorrheal pain in the e-diary. This was done daily during the pre-treatment cycle (baseline), Cycle 1, Cycle 3, and Cycle 6. If medication was used the type and dose of medication were recorded.

The median number of days with use of rescue medication reduced from 1 day at baseline and at Cycle 1 to 0 days for the remainder of the Cycles.

End point type	Secondary

End point timeframe:

Baseline to the end of the study (Cycle 1 to Cycle 6).

End point values	Estetrol / Drospirenone (E4/DRSP)			
Subject group type	Reporting group			
Number of subjects analysed	83[10]			
Units: days				
median (full range (min-max))				
Cycle 1 (N=70)	0.0 (-6 to 17)			
Cycle 2 (N=44)	0.0 (-26 to 1)			
Cycle 3 (N=67)	-1.0 (-36 to 3)			
Cycle 4 (N=33)	-1.0 (-7 to 0)			
Cycle 5 (N=20)	-1.0 (-7 to 2)			
Cycle 6 (N=38)	-1.0 (-7 to 2)			

Notes:

[10] - mITT Population

N=Evaluable number of subjects

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the day of first intake of the IP to the end of the follow-up period. Maximum overall duration to collect information on TEAEs was 191 days.

Adverse event reporting additional description:

Safety population was used for evaluation: all subjects from the Enrolled set who received at least one dose of the study treatment according to the e-Diary entries.

TEAE: any event that occurred on or after the date of first administration of study drug or, the worsening of a pre-existing event after the first administration of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Estetrol / Drospirenone (E4/DRSP)

Reporting group description:

This is a single-arm open-label study. Treatment consisted of Estetrol 15 mg /Drospirenone 3 mg (E4/DRSP) tablet. Treatment compliance was assessed based on the data entered by the subject in the e-diary.

Serious adverse events	Estetrol / Drospirenone (E4/DRSP)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 105 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Estetrol / Drospirenone (E4/DRSP)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 105 (51.43%)		
Investigations			
Lipase increased			
subjects affected / exposed	3 / 105 (2.86%)		
occurrences (all)	3		
Amylase increased			

subjects affected / exposed occurrences (all)	2 / 105 (1.90%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	 13 / 105 (12.38%) 17 2 / 105 (1.90%) 3		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain lower subjects affected / exposed occurrences (all)	 5 / 105 (4.76%) 5 4 / 105 (3.81%) 6 3 / 105 (2.86%) 4 2 / 105 (1.90%) 4		
Reproductive system and breast disorders Intermenstrual bleeding subjects affected / exposed occurrences (all) Menstruation delayed subjects affected / exposed occurrences (all) Dysmenorrhoea subjects affected / exposed occurrences (all)	 3 / 105 (2.86%) 3 3 / 105 (2.86%) 3 2 / 105 (1.90%) 2		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	 2 / 105 (1.90%) 2		

Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all)	 2 / 105 (1.90%) 3		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) COVID-19 subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Vaginal infection subjects affected / exposed occurrences (all)	 10 / 105 (9.52%) 14 4 / 105 (3.81%) 4 2 / 105 (1.90%) 2 2 / 105 (1.90%) 2 2 / 105 (1.90%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported